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Coumarin: A natural solution for alleviating inflammatory disorders

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ABSTRACT

Coumarin, a naturally occurring compound found in various plants, has a rich history of use in traditional medicine. Recent research has highlighted its anti-inflammatory properties, positioning it as a promising candidate for treating inflammatory disorders such as rheumatoid arthritis, asthma, and inflammatory bowel disease. This narrative review aims to comprehensively summarize the current knowledge regarding coumarin's pharmacological effects in alleviating inflammatory conditions by analyzing preclinical and clinical studies. The review focuses on elucidating the mechanisms through which coumarin exerts its anti-inflammatory effects, including its antioxidant activity, inhibiting pro-inflammatory cytokine production, and modulation of immune cell functions. Additionally, the paper addresses potential limitations of using coumarin, such as concerns about toxicity at high doses or with prolonged use. Before widespread clinical application, further investigation is needed to fully understand coumarin's potential benefits and risks.

1. Introduction

Inflammation, a complex and dynamic biological response to injury or infection has a vital role in healing and tissue repair (Bansal et al., 2013; Sharma et al., 2023). While inflammation is essential for healing after injury or infection, it can also be triggered and sustained by factors such as obstructed blood flow, immune system dysregulation, and chronic illnesses like metabolic syndrome and cancer (Sharma et al., 2023; Chahardehi et al., 2021; Abdulkhaleq et al., 2018). Examples of such etiologies include ischemic stroke resulting from a blood clot, exposure to polycyclic aromatic hydrocarbons, dioxin, cigarette smoke, traumatic injury or hemorrhagic stroke, Alzheimer's disease, and depression. Infections caused by viruses, bacteria, fungi, or protozoa can also elicit inflammatory reactions (Roe, 2021). Traditionally, inflammatory diseases are treated with synthetic anti-inflammatory drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. While these pharmacological agents can effectively control inflammation, they are often associated with adverse side effects such as gastrointestinal issues, cardiovascular risks, and immunosuppression (Moudgil et al., 2023). These side effects underscore the detrimental impact of an unregulated inflammatory process (Pedraza-Alva et al., 2015). Various inflammatory mediators are produced and secreted during various inflammatory reactions. In the context of human pathological conditions, significant attention has been focused on cytokines such as interferons, interleukins, and tumor necrosis factor; chemokines like monocyte chemoattractant protein 1; eicosanoids such as prostaglandins and leukotrienes; and the transcription factor nuclear factor kappa B (NF-κB), which plays a potent role in modulating inflammation (Azab et al., 2016). However, the prolonged use of anti-inflammatory and immunomodulatory agents, essential for maintaining control of chronic autoimmune reactivity, is frequently associated with significant adverse reactions and the unavoidable incurring of high drug costs (Moudgil et al., 2022).

In recent decades, interest has increased in exploring natural products, particularly plant-derived phytochemicals, as potential sources of novel therapeutic agents (Baier et al., 2020; Modarresi Chahardehi et al., 2013; Salehi et al., 2018). These natural compounds often exhibit fewer side effects than synthetic drugs, making them valuable tools for managing various ailments, including inflammatory diseases (Chahardehi et al., 2021). Intriguingly, research suggests that phenolic-rich diets may offer protection against chronic illnesses associated with oxidative stress and inflammation, including cancer, diabetes, heart disease, and neurodegenerative diseases (Shahidi et al., 2015). This highlights the potential of antioxidant compounds, especially plant-derived polyphenols, as therapeutic agents (Selamoglu et al., 2017; Rehman et al., 2021). Antioxidant compounds, with particular emphasis on polyphenol

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compounds derived from plant sources, can ease the deleterious outcomes induced by reactive oxygen species (ROS), consequently preventing chronic illnesses linked to oxidative stress and inflammation (Chahardehi et al., 2021).

Modern drug discovery increasingly focuses on natural product libraries (Adnan et al., 2020; Nageen et al., 2021), with coumarins emerging as a promising class of lead compounds for various therapeutic applications, including anti-inflammatory treatments (Koszelewski et al., 2023). Coumarin (1,2-benzopyrone or *2H*-1-benzopyran-2-one) and its derivatives, which have a fused structure of a benzene ring and α-pyrone, are a significant family of lactones (Alshibl et al., 2020). These naturally occurring, colorless, oxygenated heterocyclic compounds were first isolated from the Tonka bean (*Dipteryx odorata*) (Cuchet et al., 2024) in 1820 (Fabaceae), also called "coumaroun" locally (Kupeli Akkol et al., 2020). Coumarins, also known as benzopyrones, are a diverse group of phenolic compounds found in plants, fungi, and bacteria, including many edible species (Witaicenis et al., 2014). Their biosynthesis primarily occurs through the shikimic acid pathway, involving the conversion of cinnamic acid derived from phenylalanine metabolism (Annunziata et al., 2020). Coumarins exhibit a wide range of biological activities due to variations in their benzopyran structure. These include anti-inflammatory, antiviral, antibacterial, growth regulation, antioxidant, anticoagulant, and antitumor properties (Alshibl et al., 2020; Hamid et al., 2022; Sashidhara et al., 2011). Notably, warfarin (an anticoagulant) and novobiocin (an antibiotic) are coumarin-derived drugs (Jameel et al., 2016). Extensive research has established the anti-inflammatory potential of coumarins, with a structure-activity relationship (SAR) identified. Studies suggest that the anti-inflammatory activity is linked to an aromatic group directly attached or linked through an amide bond at the 3-position of the coumarin nucleus (Arora et al., 2014).

Chronic inflammatory diseases often require long-term management, highlighting the need for safer therapeutic options with fewer side effects compared to traditional medications (Chahardehi et al., 2022; Nisar et al., 2023). Natural products, like coumarins, offer a promising avenue (Hassanein et al., 2020). This review discussed the potential of coumarins and their derivatives as anti-inflammatory agents. Hence, this narrative review will thoroughly analyze the current research on coumarins as potential anti-inflammatory therapeutics. We will explore the fundamental mechanisms by which coumarins exert their effects, examine their effectiveness in preclinical and clinical studies, and discuss any limitations and future directions for their therapeutic use. By analyzing existing scientific data - from several databases such as PubMed, ScienceDirect, *etc*. - this review aims to deepen our understanding of coumarins from the latest data in managing inflammatory diseases and their potential for developing novel, natural anti-inflammatory therapies.

2. Inflammatory diseases

Inflammation is a critical defense mechanism, protecting the body against microbial infections, tissue injury, and physical trauma. It initiates a cascade of biochemical changes mediated by signaling molecules such as cytokines, chemokines, biogenic amines, and eicosanoids, impacting various biological processes (Kotas et al., 2015). Importantly, chronic inflammation is implicated in the development of several diseases, including obesity, cancer, and neurodegenerative disorders (Kirsch et al., 2016). The classic hallmarks of inflammation are redness, heat, swelling, pain, and loss of function at the affected site (Takeuchi et al., 2010). Orchestrating the inflammatory response is a complex interplay between various cell types, including immune cells that release cytokines, chemokines, and growth factors (Nagaraja et al., 2014). The inflammatory process involves cellular and vascular events, with the migration of white blood cells (monocytes, basophils, eosinophils, and neutrophils) and plasma to the injury site. These pathways entail the relocation of white blood cells (such as monocytes, basophils, eosinophils, and neutrophils), plasma, and fluids to the site of inflammation. These immune cells release mediators like histamine, prostaglandins, leukotrienes, free radicals, and serotonin, further amplifying the inflammatory response (Abdulkhaleq et al., 2018).

Inflammation can be categorized into acute and chronic phases, although a clear distinction may not always exist (Germolec et al., 2018). The acute phase serves as a crucial defense mechanism, with neutrophils known as polymorphonuclear leukocytes (PMNs) acting as the first responders by eliminating pathogens and cellular debris through phagocytosis (Serhan et al., 2018). The resolution of this acute phase depends on the severity of the initial injury. Chronic inflammation, however, arises from prolonged exposure to inflammatory stimuli or an abnormal response to self-antigens, leading to persistent tissue damage (Germolec et al., 2018). This chronic inflammatory state is implicated in the development of various diseases, including arthritis, cancer, cardiovascular diseases, diabetes, and neurological disorders. The underlying mechanism often involves dysregulation of signaling pathways like nuclear factor-kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3) (Kunnumakkara et al., 2018). Notably, NF-κB is critical in both acute and chronic inflammation (Chahardehi et al., 2021). Chronic inflammation is further linked to multiple stages of tumorigenesis, promoting cellular transformation, survival, proliferation, invasion, and metastasis (Singh et al., 2019). However, this phenomenon is recognized as a critical etiological factor contributing to the development of major chronic diseases, including cancer (Kunnumakkara et al., 2018). Additionally, it is recognized as a significant contributor to the development of type 2 diabetes, a metabolic disorder with an immunological component (Berbudi et al., 2020). Pro-inflammatory cytokines, specifically TNF-α, have been found to activate many intracellular signaling molecules, such as Jun N-terminal kinase (JNK) and IKKβ enzyme, which are imperative constituents of the inflammatory signaling system. As a consequence of this activation, insulin action may become impaired. Upon activation, IKKβ is known to induce the translocation of NF-κB into the nucleus, thereby promoting the upregulation of inflammatory mediators, including cytokines and chemokines (Rohm et al., 2022). Rheumatoid arthritis is a chronic, systemic, inflammatory disease primarily targeting synovial joints. The pathogenesis of rheumatoid arthritis is driven by aberrant immune responses, resulting in dysregulated secretion of pro-inflammatory cytokines (Guagnano et al., 2021). Similarly, inflammation, immune responses, and mitochondrial dysfunction are all implicated in the development of cardiovascular diseases (Ginckels et al., 2022).

Inflammation represents a tightly regulated immune response initiated to combat foreign invaders or endogenous danger signals. Pattern recognition receptors (PRRs) on immune cells recognize pathogen-associated molecular patterns (PAMPs) displayed by microbes and damage-associated molecular patterns (DAMPs) released from damaged tissues (Zeng-Brouwers et al., 2020). These PRRs include various families, such as Toll-like receptors (TLRs), C-type lectin receptors (CLRs), RIG-I-like receptors (RLRs), and NOD-like receptors (NLRs) (Chen et al., 2018a). TLRs and NLRs are particularly crucial PRRs located on the cell surface, endosomal compartments, or cytosol (Casulleras et al., 2020). Upon binding to PAMPs or DAMPs, PRRs activate signaling cascades, activating transcription factors like NF-κB and activator protein 1 (AP-1), which orchestrate the inflammatory response (Gudkov et al., 2016).

3. Treatment approach for inflammatory disorders using natural compounds from medicinal plants

The escalating burden of chronic diseases such as cancer, diabetes, and cardiovascular disease presents a formidable global health challenge (Furman et al., 2019). Despite advancements in drug discovery, identifying safe and effective therapeutic agents remains a hurdle (Thomford et al., 2018). Chronic inflammation often serves as a hallmark of these diseases, emphasizing the urgent need for innovative

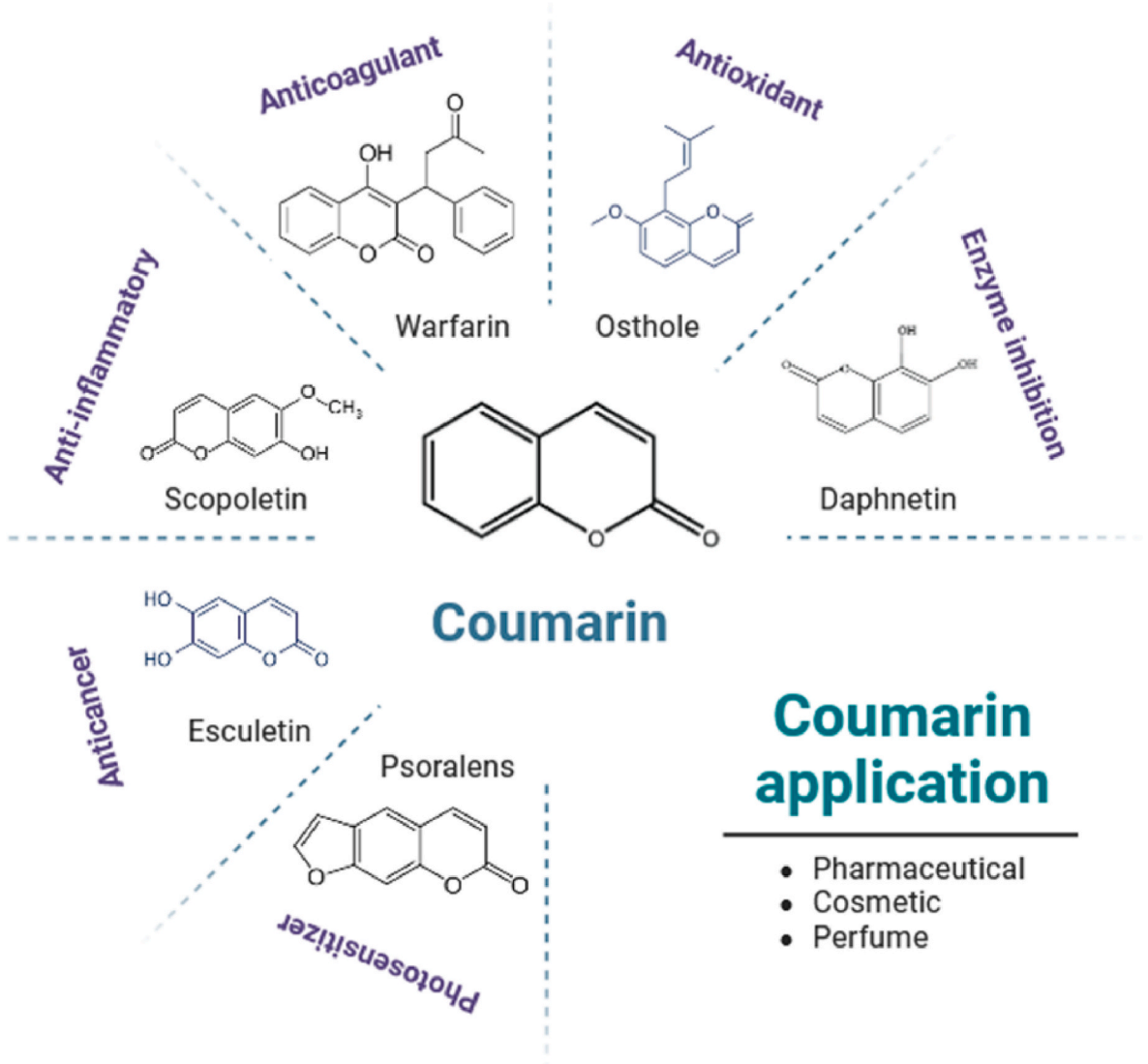

Fig. 1. Exploration of coumarin derivatives and their practical uses (adapted from Sharma et al. (2022)) (Sharma et al., 2022).

anti-inflammatory treatments (Hunter, 2012). Natural products derived from plants, animals, and microorganisms have garnered renewed attention for their potential therapeutic applications (Duan et al., 2021). These natural compounds may exist as standardized extracts or purified molecules, exhibiting demonstrably beneficial biological activities (Jenab et al., 2020). Their increasing utilization in pharmaceuticals, nutraceuticals, and cosmetics stems from their often lower incidence of side effects compared to synthetic drugs (Ekiert et al., 2020), rendering them valuable tools for developing selective agents (Baier et al., 2020). Notably, natural products offer a distinct advantage: their capacity to interact with and modulate cellular targets implicated in disease processes. Moreover, their affordability, accessibility, and generally lower risk of adverse effects render them appealing candidates for incorporation into traditional medicine (Noor et al., 2022). It is noteworthy that approximately 80% of the global population, particularly in developing nations, relies on medicinal plants for healthcare needs, underscoring their widespread utilization (Ashktorab et al., 2019). The abundance of natural resources and their potential to inspire the development of effective analogs and prodrugs further underscores the vast potential of natural products as a source of diverse and potent therapeutic agents (Pham et al., 2019).

Despite the fact that only a small fraction of natural compounds have successfully been developed into clinically approved drugs, their potential as lead structures for the development of more potent analogs and prodrugs remains considerable (Iksen et al., 2021). The documented efficacy of various plant-derived compounds in treating and preventing diseases highlights this promise. Many cultures have a long history of using medicinal plants as a primary form of healthcare, and this practice continues in many parts of the world today (Shahzad et al., 2020). Plants produce diverse natural volatile organic compounds (VOCs), often distinctive to individual species (Kim et al., 2021). For instance, green tea catechins demonstrate immunomodulatory effects by inhibiting T-cell proliferation through specific signaling pathways (Wang et al., 2021). Green tea's higher epigallocatechin-3-gallate (EGCG) and epicatechin-galate (ECG) content than black tea contributes to its enhanced antioxidant, anti-inflammatory, and anticarcinogenic properties (Vyas et al., 2021). In addition, the two galloyl-containing catechins, namely EGCG and ECG, exhibit the highest levels of biological activity. Nevertheless, the latest research indicates that EGCG may exert its effects through a wide variety of other channels, such as interacting with proteins in the plasma membrane, activating signal transduction pathways and second messengers, influencing metabolic enzymes, and even autophagy (Kim et al., 2014). Studies suggest that EGCG may have therapeutic potential against rheumatoid arthritis by suppressing matrix metalloproteinases (MMPs), enzymes involved in joint destruction during the disease (Lee et al., 2016).

Plant-derived natural compounds hold immense promise for managing inflammation by modulating key pathways and gene expression (Sharma et al., 2023). Numerous bioactive compounds have been identified for their anti-inflammatory properties, including.

- **Curcumin**: This polyphenol from turmeric potently inhibits the NF-κB signaling pathway, a crucial player in inflammation (Gupta et al., 2013).
- **Resveratrol**: It is found in grapes; resveratrol exhibits similar anti-inflammatory effects by inhibiting NF-κB and downregulating pro-inflammatory cytokines like interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNFα) (Shakibaei et al., 2012).
- **Quercetin**: Abundant in onions, quercetin acts as an antioxidant, reducing inflammation caused by oxidative stress through cyclooxygenase (COX)-2 suppression (Boots et al., 2011).
- **Gingerol**: They are extracted from ginger root, gingerols significantly inhibit COX activity, leading to decreased production of prostaglandins, which contribute to pain during inflammation (Ballester et al., 2022).

Extensive research underscores the anti-inflammatory properties of these natural compounds, highlighting their potential benefits in managing inflammatory disorders. Preclinical and clinical studies suggest they can be as effective as some conventional treatments, although further investigation into possible side effects and optimal dosages is warranted. This review has primarily focused on well-established examples. Additional exploration is warranted to investigate the anti-inflammatory potential of coumarins, another class of plant-derived compounds. As discussed earlier, coumarins exhibit diverse biological activities, and their structure-activity relationship has been associated with anti-inflammatory effects. Therefore, future research delving into the specific mechanisms of action and therapeutic potential of coumarins could lead to the development of novel and effective anti-inflammatory therapies.

4. Coumarin and its properties

Coumarins, a vast group of natural chemicals (over 800 identified), are commonly found in plants such as tonka beans and sweet clover, and are classified as benzopyrones (Kupeli Akkol et al., 2020; Ziarani et al., 2018). They exist in both free and bound (heteroside) forms and are surprisingly common, with presence in seeds, roots, and leaves across 600 plant genera and 100 plant families (Kupeli Akkol et al., 2020). Beyond their use in food additives, cosmetics, and fragrances (Eggleston, 2023). Perfumes, soaps, detergents, lotions, and even toothpaste can contain coumarin in quantities as high as 6.4% (Eggleston, 2023). Coumarins hold significant therapeutic potential due to their diverse biological activities (Kupeli Akkol et al., 2020). One particularly promising property of coumarins is their anti-inflammatory effect (Tuan Anh et al., 2017; Tosun et al., 2009). Their structure, featuring a lactone ring fused with a benzene ring, allows interaction with enzymes involved in inflammatory pathways (Tuan Anh et al., 2017; Mohammed et al., 2017), disrupting inflammatory signaling cascades and offering a natural approach to managing inflammation. Coumarins exhibit a broader range of pharmacological properties, including anticoagulant (Jung et al., 2001), antioxidant (Kadhum et al., 2011; Masuri et al., 2023), antimicrobial (Basile et al., 2009), and anticancer (El-Sayed et al., 2022) activities. Additionally, they can influence cell growth regulation pathways via signaling pathways like PI3K/Akt/mTOR (Wu et al., 2020), as depicted in Fig. 1.

While the anti-inflammatory potential of coumarins is a significant area of exploration, research is also uncovering new applications in other fields. For instance, some coumarin derivatives show promise in neurodegenerative disorders like Alzheimer's disease by inhibiting beta-amyloid aggregation, a key pathological process (Lin et al., 2022; Wojtunik-Kulesza et al., 2022). This versatility extends to the development of coumarin-based materials. Their unique optical, piezoelectric, magnetic, and electrochemical properties make them suitable candidates for various biomedical applications. These materials have potential in biosensors, tissue engineering scaffolds, and other areas (Wang et al., 2020a). These emerging trends highlight the versatility and potential of coumarin and its derivatives in various fields, including medicine, materials science, and biotechnology. Thus, due to their diverse pharmacological activities, coumarin compounds represent an interesting class of molecules that could be used alone or combined with other drugs for treating multiple diseases (Loncaric et al., 2020).

One of the most well-known pharmacological effects of coumarin is its ability to act as an anticoagulant by inhibiting vitamin K epoxide reductase (VKOR), leading to decreased clotting factors II, VII, X, and IX (Kasperkiewicz et al., 2020). This property has led to the development of synthetic derivatives such as warfarin, which are widely used clinically for preventing thromboembolic events such as deep vein thrombosis or pulmonary embolism (Lichota et al., 2020). Additionally, coumarins have shown potential anticancer activity through various mechanisms (Bisi et al., 2017). For instance, coumestrol, psoralen, isopsoralen, and 4-methoxycoumestrol are four significant classical coumarin phytoestrogen. Plant-derived phytoestrogens bind to estrogen receptors (ER) in animals and humans. Most phytoestrogens containing heterocyclic polyphenols resemble estrogens like 17β-estradiol in mammals. Phytoestrogens and ER regulate estrogen-like and anti-estrogen effects throughout life. Thus, phytoestrogens prevent and treat menopause, cardiovascular disease, osteoporosis, and breast cancer (Wang et al., 2020b). This review primarily focuses on their potential as anti-inflammatory agents.

5. The impact of coumarin in alleviation of inflammatory diseases

Coumarins, natural plant compounds, exhibit promising anti-inflammatory properties with potential applications in various inflammatory diseases. As a natural compound found in various plants, coumarin has been shown to possess anti-inflammatory properties that can help alleviate inflammatory diseases such as arthritis and asthma (Sinha et al., 2022). Their mechanism of action appears to involve multiple pathways.

- **Modulating Signaling Pathways:** Coumarins can directly interact with cellular receptors and modulate signaling cascades involved in inflammation (Kirsch et al., 2016). This disrupts the production of pro-inflammatory cytokines and enzymes, ultimately reducing inflammation.
- **Inhibiting Enzyme Activity:** Coumarins can inhibit key enzymes like cyclooxygenase (COX) and lipoxygenase (LOX), which are involved in the production of inflammatory mediators (Apweiler et al., 2022). This dampens the inflammatory response.
- **Neuroprotective Effects:** Some coumarin derivatives may offer neuroprotection by activating the tropomyosin receptor kinase B (TRKB), cAMP response element-binding protein (CREB), and brain-derived neurotrophic factor (BDNF), known as TRKB-CREB-BDNF) pathway, which promotes neuronal survival and reduces caspase activity, a marker of apoptosis (Lin et al., 2022). Additionally, they can decrease the production of reactive oxygen species (ROS), which contribute to neuroinflammation and oxidative stress (Mishra et al., 2023).

This multi-faceted approach highlights the potential of coumarins for managing various inflammatory conditions. The following sections will explore their potential benefits in diseases like neuroinflammation, edema, and inflammatory bowel disease (IBD).

5.1. Neuroinflammation

Neuroinflammation is a significant contributor to neurodegenerative diseases, imposing a considerable burden on global healthcare (Wojtunik-Kulesza et al., 2022). These intricate disorders entail protein aggregation, neurotransmitter breakdown, and other factors ultimately leading to neuronal cell death, as observed in Alzheimer's and Parkinson's diseases, both characterized by neuroinflammation (Mishra et al., 2023). Recent research unveils promising applications for coumarin derivatives in regulating neuroinflammatory pathways. New derivatives have demonstrated the inhibition of neuroinflammation by binding to the G-protein receptor GPR55, presenting a potentially safer alternative to conventional anti-inflammatory drugs while comprehensively addressing neuroinflammation (Apweiler et al., 2022; Berrino et al., 2023). Furthermore, coumarin derivatives like KIT C and KIT H have shown the capacity to reduce neuroinflammation in human and mouse cells, emphasizing their therapeutic potential in neuroinflammatory disorders (Apweiler et al., 2022). Conversely, a novel coumarin component in Murraya, MC13, exhibits interactions with LPS, inhibiting its binding to the cell membrane surface. Studies suggest that coumarin may alleviate neuroinflammation and inflammation-related neurodegenerative disorders. MC13 suppresses NF-κB activation, thereby regulating the inflammatory response and reducing the interaction of TGF-β-activated kinase 1 (TAK1)-binding protein (TAB2) with TAK1 and TNF receptor-associated factor (TRAF6), leading to decreased phosphorylation levels of NF-κB upstream regulators like IκB and IκB kinase (IKK). Additionally, MC13 significantly reduces extracellular signal-regulated kinase (ERK) and p38 MAPK phosphorylation, crucial for microglia-mediated inflammation (Zeng et al., 2015).

5.2. Edema

Edema, or swelling, commonly accompanies inflammation and can exacerbate its severity (Cui et al., 2014). Coumarins present a promising approach to managing edema, as these natural compounds have demonstrated the ability to reduce tissue swelling and inflammation (Kirsch et al., 2016). Coumarin inhibits the formation of prostaglandins by interfering with fatty acid hydroperoxy intermediates, thereby alleviating tissue swelling and inflammation, which are inhibited by coumarin and its 7-hydroxy derivative (Fylaktakidou et al., 2004). Furthermore, the clinical significance and pathogenesis of perihematomal edema (PHE), a consequence of intracerebral hemorrhage (ICH) leading to subsequent neuronal damage, have been explored. In a clinical trial by Levine et al., early relative edema was found to be less common in ICH caused by warfarin compared to ICH caused by non-coagulopathy (Levine et al., 2007). Studies investigating the intestinal anti-inflammatory effects of coumarin and 4-hydroxycoumarin in a rat model of colitis revealed their effectiveness in reducing colonic damage and edema induced by trinitrobenzene sulphonic acid (TNBS) (Luchini et al., 2008). This observed impact was attributed to the enhancement of the oxidative condition of the colon, as coumarin and 4-hydroxycoumarin hindered the reduction of glutathione, a consequence of inflammation in the colon (Luchini et al., 2008). This dual action contributes to their edema-reducing properties. Moreover, pretreatment with low doses of warfarin inhibits the development of edematous acute pancreatitis induced by cerulein in rats, thereby reducing pancreatic damage, serum enzyme levels, and inflammatory markers. Administration of warfarin at specific doses reverses the restriction of pancreatic blood flow caused by the development of acute pancreatitis (Konarska-Bajda et al., 2023).

5.3. Inflammatory bowel disease (IBD)

Chronic inflammation of the gastrointestinal system is a hallmark of inflammatory bowel disease (IBD), which includes disorders such as Crohn's disease and ulcerative colitis. Research into the anti-inflammatory effects of coumarins has shown promising results in the context of IBD. Recent studies, focusing on coumarin and 4-hydroxycoumarin (Luchini et al., 2008), have suggested their potential as adjunctive treatments for IBD due to their antioxidant and anti-inflammatory properties. These compounds have demonstrated the ability to modulate immunological and inflammatory responses while protecting against oxidative stress, two significant contributors to IBD pathogenesis (Di Stasi, 2021). Evidence from studies supports their efficacy in reducing colonic inflammation and damage, offering promise for the treatment of inflammatory bowel disease. Additionally, alkyl-substituted coumarins show promise in inhibiting enzymes involved in both inflammation and neurodegeneration (Berrino et al., 2023).

Coumarin, naturally occurring in various plants, has garnered attention for its potential to reduce inflammation and protect the nervous system (Witaicenis et al., 2014). Coumarins encompass four main groups: simple coumarins, furanocoumarins, pyranocoumarins, and pyrone-substituted coumarins (Kupeli Akkol et al., 2020). Given the prevalence of coumarin derivatives in plant-based foods and beverages in the human diet, the anti-inflammatory properties of some plant-based coumarin derivatives (scopoletin, scoparone, fraxetin, 4-methyl-umbelliferone, esculin, daphnetin, etc.) were investigated (Witaicenis et al., 2014). The following plants and their coumarin compounds exemplify this research.

- **Esculetin**: Esculetin (6,7-dihydroxychromen-2-one), found in Ash tree bark (Cortex fraxini), exemplifies the anti-inflammatory properties observed in certain coumarins. It demonstrates potent antioxidant activity, with its scavenging activity against 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals being time- and concentration-dependent (Hassanein et al., 2020). Esculetin has been shown to significantly reduce the levels of proinflammatory cytokines, including TNF-α, IL-6, IL-22, IL-23, IL-17 A, and IFN-γ. Moreover, it has been found to slow disease development in psoriatic mouse skin (Chen et al., 2018b).
- **Scopoletin**: Scopoletin (7-hydroxy-6-methoxychromen-2-one), found in plants such as *Datura metel* L. (Indian thornapple) (Chang et al., 2012) and *Artemisia scoparia* (Virgate wormwood) (Ding et al., 2008), represents another example of the investigated coumarins. Research indicates its anti-inflammatory properties, which operate through various mechanisms. These mechanisms include the suppression of T-cells, downregulation of inflammation-related genes, and inhibition of pro-inflammatory cytokine production (Ghosh et al., 2023).
- **Scoparone**: Scoparone, a natural coumarin, is found in various medicinal plant species such as *Scopolia* (Cho et al., 2016), *Artemisia* (Zhou et al., 2024), *Brunfelsia* (Mateos et al., 2022), *Solanum* (D'hallewin et al., 1999), *Mallotus* (Ding et al., 2008; Tucker et al., 2009), among others (Hassanein et al., 2020). It is notably present in *A scoparia.* Studies suggest it possesses anti-inflammatory properties by regulating various inflammatory mediators, including interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-α), and prostaglandin E2 (PGE2) (Mishra et al., 2023).
- **Imperatorin**: Imperatorin (9-(3-methylbut-2-enoxy)furo[3,2-g]chromen-7-one), a furanocoumarin (coumarin-related) compound, is abundant in *Angelica* plants such as *Angelica archangelica* and *A. dahurica* (Hassanein et al., 2020). In a study by Li et al. (2019), imperatorin demonstrated promising effects in alleviating lung fibrosis, edema, and immune cell infiltration induced by zymosan in mice. The research revealed that imperatorin acts as an anti-inflammatory agent, effectively reducing inflammation, swelling, and lung fibrosis (Li et al., 2019).
- **Umbelliferone**: Umbelliferone (4-methyl-umbelliferone) is found in *Coriandrum sativum* (Coriander) and *Salvadora persica* (Toothbrush Tree) (Sim et al., 2015).

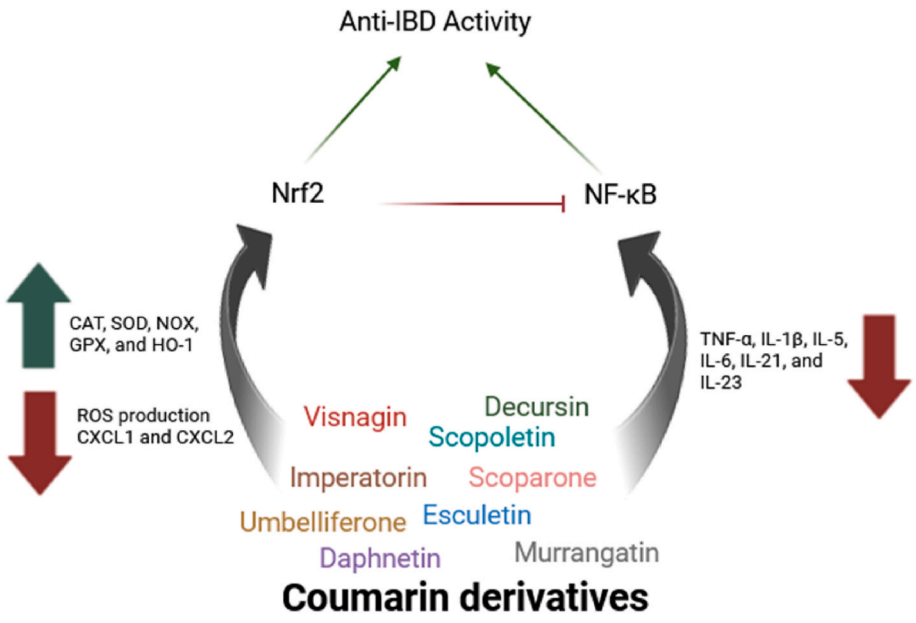

Fig. 2. Coumarin derivatives stimulate intestinal anti-inflammatory activity by acting on the Nrf2 and NF-κB signaling pathways (adapted from Di Stasi, 2023) (Di Stasi, 2023).

- **Murrangatin**: Murrangatin is a compound found in *Murraya koenigii*, commonly known as Currypatta or meetha neem (Ghosh et al., 2023). This plant contains murrangatin, an analog of coumarin, which has been found to inhibit the production of PGE2 and nitric oxide (NO) in lipopolysaccharide (LPS)-stimulated macrophages, demonstrating its anti-inflammatory activity (Mishra et al., 2023).
- **Daphnetin**: Daphnetin has demonstrated the ability to reduce the production of pro-inflammatory cytokines through various mechanisms, including regulating the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway and suppressing NF-κB signaling (Zhang et al., 2018). Shen et al. conducted a study revealing that daphnetin effectively mitigated inflammation induced by LPS and decreased the mortality rate associated with endotoxin in mice. Their findings indicated that daphnetin significantly reduced the release of TNF-α, IL-1β, IL-6, NO, and PGE2 in Raw264.7 cells. Furthermore, it downregulated the expression of iNOS and COX-2, as well as the generation of ROS (Shen et al., 2017).
- **Decursin**: Deursin, a coumarin derivative primarily derived from the roots of the medicinal plant *Angelica sinensis* (Hou et al., 2021), exhibits various biological properties, including anti-inflammatory, antioxidant, neuroprotective, and, notably, anticancer effects (Chu et al., 2024).
- **Visnagin**: Visnagin, a biologically active compound obtained from the fruits of *Ammi visnaga* (Al-Snafi, 2013) in crystalline form, has garnered attention for its potential anti-inflammatory properties (Kaul et al., 1965). Lee et al. conducted a study investigating visnagin's effects on BV2 microglial cells exposed to LPS. Their findings revealed that visnagin effectively modulates the expression of IFN-γ, TNF-α, iNOS, IL-1β, and IL-6 induced by LPS via an NF-κB-dependent mechanism while also enhancing the synthesis of the anti-inflammatory cytokine IL-10 (Lee et al., 2010). *In vivo* studies further demonstrated visnagin's potent anti-inflammatory effects with a favorable safety profile. Moreover, it exhibited selective inhibition of COX-2 *in vitro* (Khalil et al., 2019).

The research on scopoletin, scoparone, fraxetin, 4-methyl-umbelliferone, esculin, and daphnetin revealed promising anti-inflammatory properties (Witaicenis et al., 2014). These coumarin derivatives appear to achieve their effects through various mechanisms, including (Ghosh et al., 2023).

- Downregulating inflammatory genes: They can downregulate the expression of specific genes involved in inflammatory pathways.
- Suppressing T-cells: They may suppress the activity of T-cells, immune cells that can contribute to inflammation.
- Inhibiting pro-inflammatory cytokines: They can inhibit the production of pro-inflammatory cytokines, signaling molecules promoting inflammation.

The Nrf2 signaling pathway acts as regulators of oxidative stress while also exhibiting anti-inflammatory action, as demonstrated by the decrease in levels of pro-inflammatory cytokines. This effect is primarily controlled by the NF-κB signaling pathway. Hence, natural compounds that activate Nrf2, such as natural derivatives of coumarin, can exhibit both antioxidant and anti-inflammatory effects, making them highly valuable for pharmacological and therapeutic purposes in the prevention and management of IBD (Di Stasi, 2023), as illustrated in Fig. 2.

6. Molecular mechanism of coumarin's anti-inflammatory activity

The anti-inflammatory properties of coumarins, a group of chemicals with diverse biological applications, have been extensively investigated. Coumarin is believed to possess anti-inflammatory properties due to its ability to reduce tissue swelling, inhibit prostaglandin production, and modulate the immune response. Research has demonstrated that derivatives of coumarin, particularly those with 5- or 6-hydroxy or vicinal dihydroxy substitutions, effectively inhibit lipoxygenase, an enzyme involved in the synthesis of inflammatory mediators (Hadjipavlou-Litina et al., 2007). The anti-inflammatory efficacy of coumarin derivatives involves various molecular pathways and targets.

6.1. Inhibition of lipoxygenase (LOX) and cyclooxygenase (COX)

Coumarins exert their anti-inflammatory effects by inhibiting the enzymes LOX and COX, which are responsible for synthesizing prostaglandins and leukotrienes, key mediators of inflammation. By blocking these enzymes, coumarins reduce swelling and inflammation (Ghosh et al., 2023). Moreover, natural products containing 5-LOX inhibitors have been investigated for their potential as anti-inflammatory agents. Studies on various natural compounds derived from plants, including

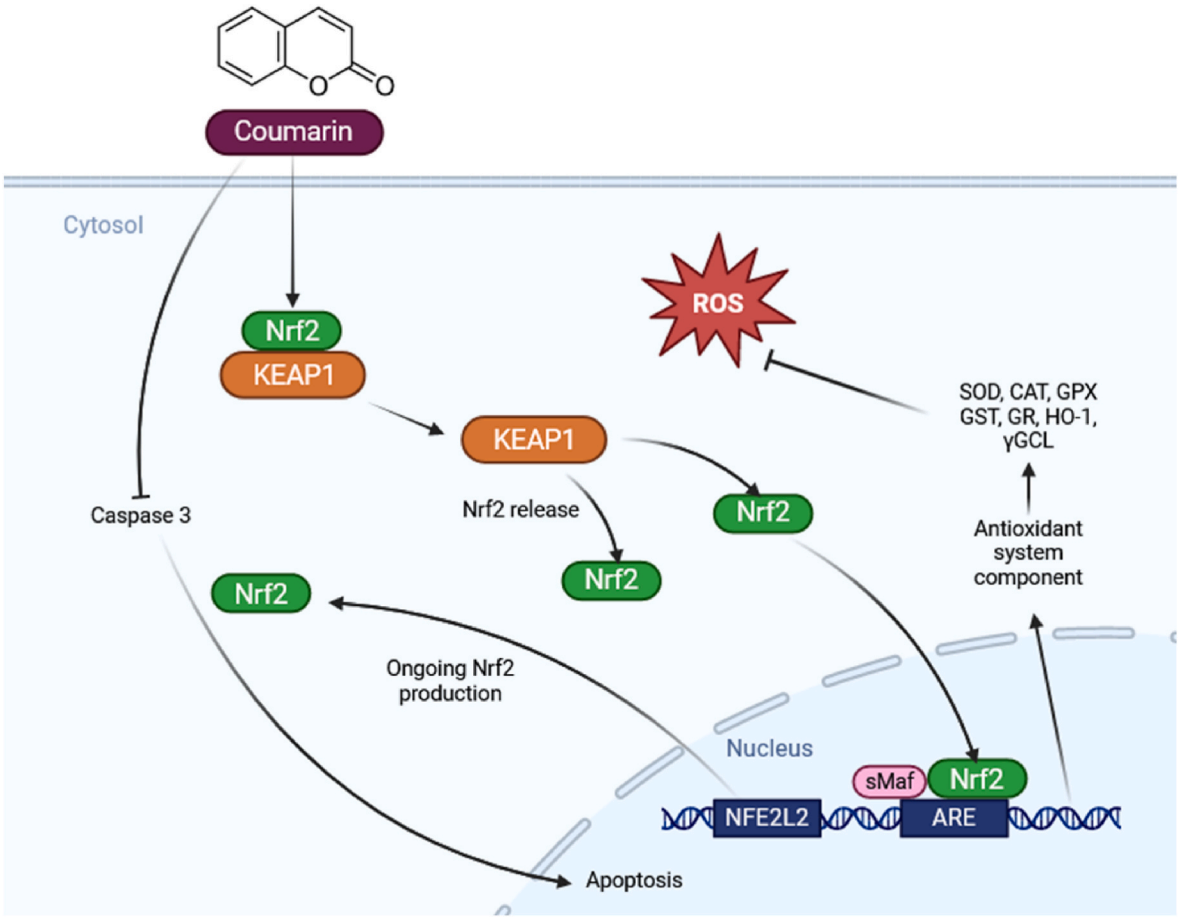

Fig. 3. Schematic illustrating the molecular pathways implicated in the antioxidant and oxidative stress response modulated by coumarin and its derivatives (adapted from Di Stasi, 2021) (Di Stasi, 2021).

coumarin derivatives, benzoquinones, phenolics, and triazole caffeic acid analogs, among others, suggest that they may possess beneficial properties as 5-LOX inhibitors (Sinha et al., 2019).

6.2. Antioxidant activity

Coumarins and their derivatives exhibit strong antioxidant activity, which is evident in their ability to scavenge free radicals like hydrogen peroxide and DPPH. This activity increases with higher coumarin concentrations, indicating a concentration-dependent effect (Al-Majedy et al., 2016). These antioxidant properties offer a two-pronged approach to managing inflammation.

1. Neutralizing free radicals: Coumarins directly neutralize ROS, which are harmful molecules produced during inflammation and can damage cells (Ghosh et al., 2023).
2. Enhancing Cellular Defenses: Coumarins act as regulators of the body's natural antioxidant system, including enzymes like glutathione peroxidase (GPX) and superoxide dismutase (SOD), catalase (CAT), superoxide dismutase (SOD), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), heme-oxygenase 1 (HO-1), thioredoxin, and the glutathione antioxidant systems consisting of glutathione (GSH) and its enzymes γ-glutamyl-cysteine ligase (γ-GCL), glutathione peroxidase (GPX), glutathione S-transferase (GST), glutathione synthetase (GSS), and glutathione reductase (GR) (Di Stasi, 2023). By supporting this system, coumarins further bolster cellular defenses against oxidative damage.

Simple coumarins, such as coumarin, 4-hydroxycoumarin, 7-hydroxycoumarin, and 7-hydroxy-4-methylcoumarin, were synthesized by Prahadeesh and associates. Their antioxidant capacity to reduce ferrous iron and scavenge peroxide was examined. The outcomes demonstrated a more than threefold improvement in peroxide scavenging upon the addition of a hydroxyl group at position 7. Ascorbic acid was the standard substance, and the effectiveness of these drugs declined in the same sequence (Prahadeesh et al., 2018). Kumar and coworkers created hybrids of 1,2,3-triazoles, 1,3,4-oxadiazole, and coumarins. They were examined for DPPH scavenging (ethanol, 30 min, room temp). One new chemical showed considerable scavenging activity (28.2% inhibition) at 40 μg/mL (Kumar et al., 2018). Synthesized pyranocoumarins, coumarin-3-sulfonamides, and coumarin-sulfonamide-chalcones were evaluated for antioxidant activity using the DPPH technique. Pyranocoumarinactivity was negligible. The same was true for chalcone-substituted substances. To compare, ascorbic acid was employed (IC_{50} = 2.83 μg/mL) (Alshibl et al., 2020). In essence, coumarins act as both scavengers and regulators of antioxidants, providing a promising strategy for mitigating inflammation and its associated cellular damage.

6.3. Activating Nrf2 signaling pathway

Coumarins exhibit a remarkable ability to interact with various cellular receptors and proteins, thereby regulating their activity and contributing to their anti-inflammatory effects. Studies have revealed that coumarin derivatives can interact with the Nrf2 signaling pathway, a system crucial for controlling antioxidant and anti-inflammatory

Table 1
Selected some medicinal plants possess coumarin and its derivatives in inflammatory disorders.

Plant/family	Common name	Type of study	Part of plant	Type of solvent	Effective compound(s)	Dose	Characteristics	Ref.
Paramignya trimera/ Rutaceae	Xao tam phan	*in vitro*	Stem	Ethanol	Ostruthin and ninhvanin	5–40 μM	Ostruthin and ninhvanin, two out of seven compounds from coumarins showed potential therapeutic effect.	Tuan Anh et al. (2017)
Artemisia capillaris/ Asteraceae	Wormwood	*in vivo*	Aerial parts	Ethanol	Esculetin	6.6 μM	The edematic response was significantly suppressed by esculetin. In mice, both aerial parts and esculetin suppressed the delayed-type hypersensitivity response.	Kwon et al. (2011)
Daphne odora/ Thymelaeaceae	Winter daphne	*in vivo*	–	–	Daphnetin	20–80 mg/kg	The extract showed that p-AKT inhibition was responsible for the downregulation of NF-kB expressions, while it had no effect on p-ERK1/2.	Kumar et al. (2016)
Angelica sinensis/ *Apiaceae*	Female ginseng/dong quai	*in vitro* and *in vivo*	Roots	–	Glabralactone	5 and 10 mg/kg	Glabralactone blocked LPS-stimulated RAW264.7 macrophage nitric oxide generation. It was reported to downregulate LPS-induced iNOS, TNF-α, IL-1β, and miR-155 mRNA and protein expression. It also substantially reduced NF-κB and TRIF-dependent IRF-3 pathway activation in LPS-stimulated macrophages. In carrageenan-induced rats, glabralactone (5 and 10 mg/kg) showed anti-inflammatory action, reducing paw edema volume and suppressing iNOS and IL-1β signaling in paw tissues.	Choi et al. (2022)
Cortex fraxini	Qingpi	*in vivo*	–	–	Esculin	5–20 mg/kg	Esculin lowered pro-inflammatory cytokine levels of TNF-α and IL-6 in supernatant *in vitro*. In peritoneal macrophages, esculin dramatically reduced LPS-induced MAPK pathway activation.	Niu et al. (2015)
Aegle marmelos (Linn)/ Rutaceae	Japanese bitter orange, Bael, Bengal quince, golden apple, stone apple or wood apple	*in vivo*	Fruits	Methanol	Imperatorin	5–10 mg/kg	Pretreatment with imperatorin dramatically reduced levels of oxidative stress and AChE while also reversing behavioral and memory abnormalities caused by LPS. Additionally, it resulted in a considerable increase of BDNF levels and decreased TNF-α and IL-6 levels.	Chowdhury et al. (2018)
		in vitro and *in silico*	Fruits	Ethanol, methanol, ethyl acetate, Dimethylsulfoxide (DMSO) and chloroform	0.72% aegeline, 1.2% marmelosin, 8.9% marmesin, 2% scopoletin, 1.7% umbelliferone, and 4% psoralen,	100–1000 μg/mL	Marmelosin and marmesin had the strongest activity against the enzymes targeted for the aforementioned tests, and *in silico* and *in vitro* analyses confirmed that the enriched extract of Aegle marmelos fruit was a powerful anti-inflammatory and anti-diabetic agent.	Tiwari et al. (2023)
Ammi majus L./ Apiaceae	Queen Anne's lace	*in vivo*	Aerial parts	Hexane	6-hydroxy-7-methoxy-4 methyl coumarin and	0.01 mg/100 g	Two compounds were found to be effective in anti-inflammatory activity.	Selim et al. (2012)

responses (Di Stasi, 2023). Nrf2, along with its inhibitor Kelch-like ECH-associated protein 1 (Keap1), plays a pivotal role in regulating oxidative stress, and activating these proteins has emerged as a promising approach for treating or preventing various acute and chronic disorders. Moreover, activation of the Nrf2/Keap1 signaling pathway leads to the suppression of NF-κB, a transcription factor associated with generating pro-inflammatory cytokines, thereby supporting an anti-inflammatory response. Several natural coumarins have been identified as potent antioxidants and intestinal anti-inflammatory agents, exerting their effects through diverse pathways, primarily by modulating the Nrf2/Keap1 signaling pathway (Di Stasi, 2023).

Daphne odora Thumb., commonly known as winter daphne, belongs to the Thymelaeaceae family of plants and contains daphnetin (7,8-dihydroxy-coumarin) as its primary coumarin derivative. Daphnetin, a fundamental coumarin, possesses numerous pharmacological uses and primarily functions as an antioxidant by influencing the Nrf2 signaling pathway, among other pathways. In a model of 7,12-dimethylbenz(a) anthracene-induced breast carcinogenesis in female Sprague Dawley rats, intraperitoneal administration of daphnetin at dosages of 20, 40, and 80 mg/kg protected against lipid peroxidation and improved antioxidant indicators such as SOD, CAT, GPX, and GSH (Kumar et al., 2016). Daphnetin elevated Nrf2 and HO-1 expressions while concurrently downregulating NF-κB and reducing the production of pro-inflammatory cytokines TNF-α and IL-1β in a model of cisplatin-induced nephrotoxicity in C57BL/6 mice, with doses of 2.5, 5, and 10 mg/kg administered intraperitoneally (Zhang et al., 2018). Additionally, by reducing ROS formation, daphnetin inhibited LPS-induced inflammatory cytokine production *in vitro* (Zhang et al., 2018), as depicted in Fig. 3.

6.4. Structure-activity relationship (SAR)

Many investigations have explored coumarins' structure-activity relationship (SAR) to elucidate their anti-inflammatory mechanisms. For instance, electron-rich hydrophobic groups at C-3 and unsaturated heterocyclic rings at C-4 are examples of nitrogen-containing heterocycles that could potentially enhance the anti-inflammatory effects of coumarins (Bansal et al., 2013). Table 1 showcases the presence of coumarin and its derivatives in various medicinal plants, highlighting their anti-inflammatory properties.

The coumarin chemical glabralactone, derived from *A. sinensis*, demonstrates anti-inflammatory effects by inhibiting TRIF-dependent IRF-3 signaling and NF-κB pathways. Choi et al. found that glabralactone can potentially treat inflammatory diseases based on its *in vitro* and *in vivo* anti-inflammatory effects (Choi et al., 2022). Additionally, esculin, by suppressing NF-κB expression and activating Nrf2/HO-1 signaling, alleviated acute liver injury in mice induced by LPS/D-galactosamine, as demonstrated by research conducted by Liu et al. on the effects of esculin on Nrf2 activation (Liu et al., 2018).

Overall, coumarin exhibits potential as a safe alternative treatment option due to its ability to inhibit pro-inflammatory cytokines and counteract oxidative stress. However, further clinical trials are necessary to determine optimal dosages, efficacy, and safety profiles before widespread recommendation.

7. Future direction

While the study highlights the potential anti-inflammatory effects of coumarin and its derivatives, further research is needed to explore several aspects. Future investigations should prioritize the following areas.

1. Comprehensive Clinical Trials: Conducting extensive clinical trials to determine the most effective doses, efficacy, and safety profiles of coumarin-based medications for treating specific inflammatory conditions. This will help assess their suitability for widespread therapeutic use.
2. Combined Effects Studies: Investigate the synergistic effects of coumarin with other natural or synthetic anti-inflammatory drugs to determine if they complement each other in a mutually beneficial manner. This integrative approach can enhance overall therapeutic efficacy while minimizing adverse effects.
3. Structure-Activity Relationships (SAR): In-depth analyses of the structure-activity relationships of coumarin derivatives are performed to identify more potent and specific molecules with improved pharmacokinetic properties.
4. Novel Delivery Systems: Developing innovative delivery systems or formulations to enhance the absorption and precise targeting of coumarin-based drugs for therapeutic purposes.
5. Molecular Mechanisms Elucidation: Determining the specific molecular mechanisms through which coumarin and its derivatives exert their anti-inflammatory effects, focusing on their interactions with key signaling pathways and transcription factors involved in the inflammatory response.

8. Conclusion

In conclusion, this review thoroughly examines the anti-inflammatory properties demonstrated by coumarin and its derivatives. Existing evidence suggests that coumarin possesses a diverse range of pharmacological properties, including antioxidant, neuroprotective, and anti-inflammatory effects. These attributes position coumarin as a promising therapeutic candidate for various inflammatory disorders. However, further investigation is necessary to fully understand its mechanisms of action, refine its therapeutic applications, and address any potential safety concerns associated with its use. By addressing these gaps, coumarin-based compounds could emerge as beneficial natural alternatives or adjuncts to conventional anti-inflammatory treatments, offering a safer and more effective approach to managing chronic inflammatory conditions.

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Farnoosh Saadati: wrote first draft, helped in providing data. **Amir Modarresi Chahardehi:** wrote first draft, planned, supervised the study and edited the manuscript, checked the latest version of manuscript. **Negar Jamshidi:** helped in providing data. **Nazanin Jamshidi:** helped in providing data. **Darioush Ghasemi:** organized the draft and checked the first draft, checked the latest version of manuscript, All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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